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Original Research

The Role of 4D-CT for Pre-Operative Localization in Patients with Primary Hyperparathyroidism with Negative Ultrasonography and/or Sestamibi SPECT/CT

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ABSTRACT

Objectives: The major cause of primary hyperparathyroidism (pHPT) is parathyroid adenoma. Today, minimally invasive parathyroidectomy (MIP) has become the standard treatment for patients in whom the pathological gland can be localized with pre-operative imaging methods. In this study, we aimed to evaluate the role of 4D-CT in pre-operative localization in patients with pHPT who are negative for ultrasonography (USG) and/or sestamibi single-photon emission computed tomography/CT (SPECT/CT) and will undergo primary surgery.

Methods: Patients whom were operated between 2018 and 2023 were included to this study. 4D-CT results of patients with one- or two-negative USG and SPECT/CT results were evaluated retrospectively.

Results: In this study, 19 patients (5 men and 14 women) with a mean age of 57.1±8.5 years were evaluated. Pathology results were consistent with parathyroid adenoma in 18 patients (94.7%) and parathyroid hyperplasia in 1 patient (5.3%). USG was negative in six patients, SPECT/CT was negative in 14 patients, and both were negative in four patients. In 4D-CT, positive images were detected in 15 patients and these results were finalized as true positive in 14 patients and false positive in 1 patient. The sensitivity of 4D-CT was 82.4% (95% CI: 60.4–95.3%), positive predictive value was 93.3% (95% CI: 73.8–99.6%), accuracy was 78.9%, and localization rate was 73.7%. In 14 (73.7%) patients, the pathological glands were removed by MIP.

Conclusion: In approximately 75% of patients with negative USG and/or SPECT/CT, the pathological gland can be localized with 4D-CT and MIP can be applied in these patients.

Key words: 4D-CT, parathyroid adenoma, primary hyperparathyroidism

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Primary hyperparathyroidism (pHPT) is the third most common endocrine disease after diabetes mellitus and hypothyroidism, and its only curative treatment is surgery. The surgical treatment of pHPT has undergone extensive change over the past 2–3 decades.[1] Although bilateral neck exploration (BNE) is still the gold standard operative approach in the surgical treatment of pHPT, currently minimally invasive parathyroidectomy (MIP) methods have become the standard treatment option which is used in selected patients with positive imaging due to the fact that the pathological cause of pHPT is single-gland disease in 85% of the patients and the increased availability of pre-operative localization studies.[2] MIP is the first choice in the treatment of pHPT in patients with an enlarged solitary adenoma localized preoperatively. Since every patient with sporadic pHPT with surgical indication is a potential MIP candidate, pre-operative imaging methods are used as standard to preoperatively localize the enlarged glands, plan, and apply the appropriate operation.[3]

Ultrasonography (USG) and sestamibi scintigraphy are widely used as the first-stage imaging methods, often combined, and considered as the optimal combined option.[3,4] In the meta-analysis of pre-operative imaging modalities, the pooled sensitivity rates for USG and sestamibi scintigraphy were 76.1% (95% confidence interval, 70.4–81.4%) and 78.9% (64–90.6%), respectively, pooled positive predictive values (PPV) for those were 93.2% (90.7–95.3%) and 90.7% (83.5–96.0%), respectively.[5] Sensitivity rate increases when scintigraphy is combined with single-photon emission computed tomography (SPECT).[6] Combining USG and nuclear medicine imaging modalities increase the sensitivity rate.[7] However, these localization studies are negative in 12–24% of cases and inconsistent in 24–27% of cases.[8]

Four-dimensional computed tomography (4D-CT) was first applied in 2006 as a new option for pre-operative localization.[9] Many subsequent studies have showed the superiority of 4D-CT to USG and scintigraphy regarding the diagnosis.[10] Despite the known advantages of 4D-CT over conventional imaging modalities, USG and scintigraphy, there is no consensus on its role in the pre-operative imaging algorithm. Some studies have suggested that 4D-CT should be the first-line imaging tool for pre-operative localization for pHPT; other studies have recommended its use as a second-line imaging tool in case of the failure of the other imaging modalities.[11]

To apply MIP, it is necessary to localize the abnormal pathological gland with pre-operative localization studies. Up to 95% of cases with positive localization in pre-operative imaging methods are related to single-gland disease.[12] In patients with negative scintigraphy and/or USG, 4D-CT scan can detect abnormal glands in more than half of these cases, making a significant contribution to the localization.[13] Despite strong evidence for the superiority of 4D-CT in parathyroid gland localization, its use in pre-operative imaging varies widely and is significantly lower than the use of USG and scintigraphy.[11]

In this study, we aimed to evaluate the contribution of 4D-CT to the localization of the pathological parathyroid glands in patients with negative USG and/or sestamibi scintigraphy (SPECT/CT).

Methods

In this study, the data of the patients with the diagnosis of pHPT were evaluated retrospectively. Patients who underwent 4D-CT between 2018 and 2023 due to the negative USG and/or SPECT/CT were included in the study. Approval for the study was obtained from the Local Ethics Committee. The contribution of 4D-CT imaging to pathological gland imaging and focused surgery was evaluated. Patients with the previous neck surgery or parathyroid surgery, familial hyperparathyroidism, multiple endocrine neoplasia, renal failure, contrast allergy, pregnant patients, patients with secondary and tertiary hyperparathyroidism, and patients with missing data were excluded from the study.

Localization Study

Routine USG and sestamibi SPECT/CT are performed preoperatively to all patients with the diagnosis of pHPT in our clinic. Since 2018, 4D-CT has been applied to the patients with one or two negative imaging scans, and without contraindications for CT scanning and contrast allergy. USG was performed by an experienced radiologist (AO). Sestamibi SPECT/CTs were reported by an experienced nuclear medicine specialist.

In our center, 4D-CT was applied with Siemens Somatom Definition Edge 128 section 128 detector CT device (Siemens AG, Munich, Germany) using the following parameters: tube voltage of 100 kVp, tube current of 271 mAs, CTDIvol 10.3 mGy, DLP:243 mGt*cm, collimation of Acp. 128*0.6 mm; pitch of 0.8, rotation of 0.5 s, matrix of 512, slice thickness of 1 mm and increment of 1.0 mm, tilt: 15–16, scan time 7.16–8 s, delay 2 s, and direction: caudocranial. After pre-contrast images were taken, 75 mL of nonionic contrast agent (350 mg/100 mL) was injected intravenously through the right cubital vein at a rate of 4.5 m/s, followed by 35 cc saline at a rate of 4.5 mL/s. Thin axial 1-mm sections were taken from the mandible to the level of the tracheal bifurcation. Contrast-enhanced series of images were acquired in the arterial phase (20–25 s. after the contrast medium injection), venous phase (60–70 s after the contrast medium injection). Images were evaluated by a specialist radiologist (AG) experienced in head and neck radiology. Pathological parathyroid glands were defined according to their anatomical structures, diameters, and contrasting patterns.

The accuracy of 4D-CT for localization was evaluated. If the pathological gland was found in the localization that 4D-CT demonstrated and surgical cure was achieved by removing that pathological gland, it was defined as true positive. If the pathological gland was detected in a different localization other than the 4D-CT pointed out, it was defined as false positive. Additionally, if not any pathological gland could be localized through 4D-CT and solitary pathological gland was detected during exploration, it was defined as false negative. However, it was defined as true negative if multiple gland disease was detected.[14] The rates of localization of pathological glands, sensitivity, PPV, and accuracy were calculated for 4D-CT. The formulas were 100*(true positive (n)/total n) for localization ratio, true positive/(true positive + false negative) for sensitivity, and true positive/(true positive + false positive) for PPV. Pre-operative biochemical diagnosis was made in all patients, and since no imaging method was used to confirm or exclude the diagnosis, the specificity and negative predictive value of 4D-CT were not calculated as these are not clinically significant.

Surgery

In our clinic, focused approach (FA) or unilateral neck exploration (UNE) on the pathological gland was applied to patients with positive and compatible two imaging scans through lateral approach. UNE was applied to patients with a single positive imaging. BNE was performed in patients with two negative or inconsistent imaging scans. UNE was converted to BNE when no pathological gland could be detected on the side with positive imaging in FA or UNE, when two normal glands were seen, or two enlarged glands were present. FA or UNE is usually performed with the open method and the minimally invasive focused lateral approach. This method was defined as MIP. MIP is performed through a 2.5–3 cm incision between the anterior edge of the sternocleidomastoid muscle (SCM) and strap muscles and reaching the thyroid region along the medial side of the carotid sheath. To perform BNE, the lateral incision is extended across the midline and converted to the standard Kocher incision. The contralateral thyroid region is usually entered from the midline or sometimes using the lateral approach through the medial of the SCM.

Intraoperative PTH Measurement

In all patients, blood samples were taken from the peripheral vein for PTH measurement at pre-excisional, post excisional 10 and 20 min, and PTH measurement was accelerated in the central laboratory. When the pathological gland was detected in the localization compatible with the two positive imaging pointed out, the surgery was terminated without waiting for the intraoperative PTH result. If one large gland and one normal gland compatible with the imaging were detected in patients who underwent UNE with a single positive imaging, the surgery was terminated without waiting for the intraoperative PTH result. If FA was applied in a patient with single positive imaging and pathological gland was compatible with the imaging study, or if UNE was applied and a pathological gland was found, but the other gland on the same side was not detected, the intraoperative PTH result was awaited, and the decision was made according to the PTH result. The surgical procedure was converted to BNE in case of insufficient decrease in PTH level.

Intraoperative quick PTH measurement is not available in our center, intact PTH measurement is analyzed in the central laboratory with the Cobas 8000 (Roche Diagnostics GmbH, Mannheim, Germany) device by sandwich electrochemiluminescence immunoassay method, it takes approximately 25–30 min, and the results are given as pmol/L (Reference range is 15–65 ng/L (1.6–6.9 pmol/L). Ca and PTH measurements were performed on the 1st post-operative day in all patients, and normocalcemic patients were discharged. If there is not enough PTH decrease in the post-operative evaluation of intraoperative PTH values and/or hypercalcemia persists, these patients are evaluated early in terms of persistent disease and additional imaging method is applied in the early period and a surgical strategy is planned accordingly. If the surgeon could not decide whether the excised tissue was parathyroid or not, or could not discriminate from other tissues, the specimen was evaluated by frozen examination. Surgical success was defined as the decrease of PTH level below the upper limit of the normal reference values on intraoperative PTH measurements and on the 1st post-operative day and achieving normocalcemia.

The patients were followed up in the outpatient clinic at the 1st week, 1st, 3rd, and 6th months postoperatively. Surgical cure was defined as achieving normocalcemia and maintaining it for 6 months in patients with a follow-up of 6 months or more. Persistent disease was defined as the persistence of hypercalcemia or re-occurrence of hypercalcemia within the first 6 months after surgery. Re-emergence of hypercalcemia after 6 months of normocalcemia was defined as recurrent disease.[1]

Results

The data of 19 patients (5 F, 14 M) with a mean age of 57.1±8.5 years were evaluated retrospectively in the pres-

Table 1. Descriptive information of patients who were included to this study

	n (%)
Gender	
Female	14 (73.7)
Male	5 (26.3)
	Mean±SD (min–max)
Age (years)	57.1±8.5 (38–71)
Pre-operative serum levels	
Creatinine (mg/dL)	0.73±0.19 (0.52–1.23)
Parathormone (ng/L)	153.13±124.27 (74.3–613.0)
Calcium (mg/dL)	11.04±0.76 (9.9–12.4)
Magnesium (mg/dL)	2.13±0.12 (1.8–2.3)
Phosphorus (mg/dL)	2.79±0.48 (2.1–3.7)
Alkaline phosphatase (U/L)	100.79±32.65 (50–168)
Serum levels at post-operative day 1	
Parathormone (ng/L)	24.85±17.29 (1.4–63.3)
Calcium (mg/dL)	8.56±0.78 (7.3–10.5)
Magnesium (mg/dL)	1.92±0.17 (1.8–2.4)
Phosphorus (mg/dL)	3.39±0.58 (2.4–4.2)
Alkaline phosphatase (U/L)	103.0±31.46 (65–155)
Mean follow-up time (months)	3.9±4.5 (0–16)
Serum levels at last follow-up	
Creatinine(mg/dL)	0.78±0.20 (0.54–1.29)
Parathormone (ng/L)	53.79±25.97 (10.0–126.7)
Calcium (mg/dL)	9.19±0.45 (8.2–10.1)
Phosphorus (mg/dL)	3.52±0.62 (2.4–5.0)
Alkaline phosphatase (U/L)	95.17±33.95 (58–176)
Pathology results	
Parathyroid adenoma	18 (94.7)
Parathyroid hyperplasia	1 (5.3)
Parathyroid gland volume (cm^3)	0.98±1.14 (0.07–3.90)

SD: Standard deviation.

ent study. The general data of the patients are given in Table 1. According to the pathology results, single-gland disease (parathyroid adenoma) was detected in 18 patients (94.7%), and multi-gland disease (parathyroid hyperplasia) was found in 1 patient (5.3%).

Scintigraphy was negative in 14 (73.7%) and positive in 5 (26.3%). Of the positives, 4 (80%) were true positive (three single-gland disease and one multi-gland disease) and 1 (20%) was false positive (one single-gland disease). The localization rate of scintigraphy was 27.7%. On USG, positive focus was detected in 10 patients (52.6%) of which seven were strongly positive and three were suspiciously positive. Of these, nine were true positive (90%) and one was false positive (10%). The localization rate of USG was 47.4%. In four patients, both USG and sestamibi SPECT/CT were negative.

Table 2. The distributions of TP, FP, TN, and FN findings in 4D-CT

TP	FP	TN	FN	Total number of patients
14	1	1	3	19

TP: True positive; FP: False positive; TN: True negative; FN: False negative.

The comparison of 4D-CT images with intraoperative findings and the numbers of true positive, false positive, true negative, and false negative is given in Table 2. The sensitivity of 4DBT was 82.4% (95% CI: 60.4–95.3%), PPV was 93.3% (95% CI: 73.8–99.6%), and accuracy was 78.9%. Localization rate was 73.7%.

During the operation, MIP (FA or UNE) was applied to 15 patients using the lateral approach. In 14 (73.7%) patients, the pathological gland was found on the operation side and the operation was terminated. BNE was performed in a total of five patients. BNE was performed directly in three patients with negative imaging. BNE was performed in one patient with USG and 4D-CT positive, since lobectomy would be performed on the contralateral side. In one patient, it was converted to BNE, because no pathological gland could be found. The pathological gland was found on the opposite side. Adequate PTH reduction was achieved in all patients with intraoperative PTH measurement. On post-operative day 1, all patients were discharged with normal or lower than normal PTH values.

Hypoparathyroidism developed in 1 patient (20%) who underwent bilateral exploration. PTH value is 10 pg/mL in 4 months follow-up and follow-up continues with calcium replacement. Unilateral vocal cord paralysis (4.2%) developed in one patient out of 24 recurrent laryngeal nerves at risk in 19 patients.

Discussion

4D-CT application in pre-operative imaging is gradually increasing as first-line or second-line imaging. In our center, 4D-CT has been applied as second-line imaging to date. In our study, the effectiveness of 4D-CT was evaluated in patients in whom one or both of SPECT/CT and USG were negative. According to our results, the pathological gland localization rate with 4D-CT was 73.7%, sensitivity was 82.4% (95% CI: 60.4–95.3%), PPV was 93.3% (95% CI: 73.8–99.6%), and accuracy was 78.9%. In our study, the localization rate of SPECT/CT was 27.7%, the localization rate of USG was 47.4%, and the localization rate of 4D-CT was higher. Since all patients with pHPT who underwent USG and SPECT/CT were not included in the study, and patients with at least one negative imaging from USG and SPECT/CT were selected, the sensitivity, PPV, and accuracy of scintigraphy and USG were not calculated. In our study, with the contribution of 4D-CT, adequate PTH reduction and normocalcemia were achieved surgically in 73.7% of patients with MIP. If there was no indication for thyroid-related surgery in the patient who underwent lobectomy on the contralateral neck, the MIP rate would have been 78.9% by performing FA in this patient. In the literature, there are a few studies in which 4D-CT was evaluated in studies where the pathological gland could not be localized with scintigraphy and USG. When these studies are evaluated, it is noteworthy that our study is among the studies with high sensitivity, PPV, and accuracy.

Seeliger et al.[15] reported that the pathological gland could be accurately localized with thin-section CT or 4D-CT in 13 (52%) of 25 patients in whom standard imaging methods were suspicious or negative, and parathyroidectomy with FA could be performed in 11 of these 13 patients. They emphasized that FA can be performed in selected patients with the contribution of CT. In another recent study, the rate of correct lateralization and localization of pathological glands in 64 patients who could not be localized or discordant in USG and scintigraphy imaging were 57.8% and 48.4% with 4D-CT, respectively, and was found higher from USG (31.1% and 18%, respectively) and scintigraphy (32.7% and 28.6%, respectively). The authors emphasized that this is acceptable, and that 4D-CT should be considered as second-line imaging.[16] Lubitz et al.[13] found the rates of lateralization and localization of abnormal parathyroid glands with 4D-CT as 73% and 60%, respectively, in 60 patients who were poorly localized (negative, discordant, or inconclusive) by USG and scintigraphy. In 4D-CT, the accuracy is 70% in the presence of a single lesion, while the accuracy drops to 29% when multiple lesions are detected (p=0.03). They emphasized that more than half of the poorly visualized lesions can be detected with 4D-CT, and 4D-CT should be considered in patients with negative or inconsistent USG and scintigraphy.

Tian et al.[17] retrospectively evaluated the data of patients who underwent parathyroidectomy for pHPT between 2004 and 2015. After 2011, 4D-CT was applied to patients over 50 years of age whose sestamibi SPECT scintigraphy and USG were discordant. They applied 4D-CT to 100 patients and found the sensitivity of 4D-CT (72.9%) higher than SPECT scintigraphy (48.3%) and USG (52.3%) in these patients. However, there was no difference in the center's initial cure rates of patients before and after 4D-CT (95.4% vs. 95.9%, p=0.85), and MIP (74.5 vs. 79.9%, p=0.22) rates. Although the introduction of 4D-CT as a second-line imaging modality in pHPT did not change the initial cure rates or MIP rates, the authors reported that 4D-CT may assist in surgical planning in patients with pHPT in whom SPECT scintigraphy and US findings are discordant.

Day et al.[18] found the sensitivity of 4D-CT to localize an abnormal parathyroid gland as 89% and PPV as 74% in patients with pHPT in whom the pathological gland could not be localized by USG and scintigraphy. They found a higher rate of focused unilateral approach in patients with negative scintigraphy and USG compared to those who did not undergo 4D-CT (38% vs. 19%, χ^2=3.0, p=0.041). Hinson et al.[19] found the sensitivity and accuracy of 4D-CT for localization in pHPT patients that could not be localized by USG and scintigraphy as 84.2%, 82.9% in the correct side on the neck, and 76.5% and 88.2% in the correct quadrant, respectively. The authors found the radiation dose of 4D-CT lower than SPECT/CT scintigraphy in the shooting protocol they applied and they reported that 4D-CT may be considered as a first-line and second-line imaging method.[19]

Similar to the contribution of the localization of the pathological gland that cannot be localized in other studies, the benefits of 4D-CT have also been demonstrated in other conditions. These are other difficult conditions that can be challenged in patients with pHPT such as normocalcemic HPT, patients with low baseline parathormone value, multiple gland disease, ectopic glands, small glands, and recurrent or persistent HPT, and it has been demonstrated to be a superior localization method in patients who have had previous neck surgery.[17,20-27] Although 4D-CT is a better method for localization in multi-gland disease compared to other imaging modalities, it should be kept in mind that its sensitivity is lower than that of single-gland disease.[27] It has also been revealed that 4D-CT has a high pre-operative negative predictive value (93.3%). In the majority of cases, a quadrant without 4D-CT radiographic evidence of suspicious for parathyroid adenoma is unlikely to harbor biochemically significant parathyroid lesions. It was emphasized that BNE can be safely avoided in patients with confirmed solitary gland disease.[28] Eller et al.[14] reported that 4D CT was the most appropriate imaging modality in pre-operative imaging.

The most recent meta-analysis, which included 16 studies, containing six first-line, nine second-line, and one both first-line and second-line evaluations, included 1032 patients. In patient-based analysis, pooled sensitivity of 81% (95%CI: 70–90%) with heterogeneity (I2=81.9%) and pooled PPV of 91% (95%CI: 82–98%), with heterogeneity (I2=80.8%) was detected. In subgroup analysis of patient-based analysis, second-line and first-line imaging, the pooled sensitivity was 77% (95%CI: 67–86%) and 86% (95%CI: 62–100%), and pooled PPV was 94% (95%CI: 86–100%) and 86% (95% CI: 68–98%), respectively. In the lesion-based analysis, the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratios of 4D-CT were 75% (95%CI: 66–82%), 85% (95%CI: 50–97%), 4.9

(95% CI: 1.1–21.3), 0.30 (95%CI: 0.19–0.45), and 17 (95%CI: 3–100), respectively. The authors emphasized that 4D-CT has moderate sensitivity and specificity in the pre-operative localization of pathological parathyroid glands, both in patient and lesion-based analysis, and its performance can be increased when it is used as a first-line modality.[29]

The limitations of our study are that it is a retrospective study with limited number of cases and the post-operative follow-up period is short. However, we think that the inclusion of only the cases with primary surgery and forming a homogeneous group is an important advantage in terms of the results of the study.

Conclusion

In approximately 75% of patients with negative USG and/or SPECT/CT, the pathological gland can be localized with 4D-CT and MIP can be applied in these patients.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Sisli Hamidiye Etfal Hospital (No: 2283, dated 18.04.2023).

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Conflict of Interest: None declared.

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